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Mortality Rates and Causes of Death in a Cohort of HIV-Infected and Uninfected Women, 1993–1999

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ABSTRACT *HIV/AIDS-associated and non–HIV/AIDS-associated death rates and causes of death between 1993 and 1999 were examined in 885 HIV-infected women and 425 uninfected women of the HIV Epidemiology Research Study cohort. Causes of death were determined by review of death certificates and the National Death Index. Adjusted hazard ratios were calculated for mortality risk factors. In the 885 HIV-infected women and 425 uninfected women, 234 deaths and 8 deaths, respectively, occurred by December 31, 1999. All-cause death rates in the HIV-infected women were unchanged between the pre-HAART (1993–1996) and HAART eras (1997–1999)—5.1 versus 5.4 deaths per 100 person-years (py). AIDS as a cause of death decreased from 58% of all deaths in 1996 to 19% in 1999, while HAART use increased to 42% by the end of 1999. In spite of the modest proportion ever using HAART, HIV-related mortality rates did decline, particularly in women with CD4+ cell counts less than 200/mm^3. Drug-related factors were prominent: for the 129 non–AIDS-defining deaths, hepatitis C positivity (relative hazard [RH] 2.6, $P < .001$) and injection drug use (RH 1.7, $P = 0.02$) were strong predictors of mortality, but were not significant in the Cox model for 105 AIDS-defining deaths (RH 0.9, $P > .30$ and RH 0.7, $P > .30$, respectively. The regression analysis findings, along with the high percentage of non-AIDS deaths attributable to illicit drug use, suggest that high levels of drug use in this population offset improvements in mortality from declining numbers of deaths due to AIDS.*

KEYWORDS *Women, Mortality, Cause of death, HIV, AIDS, Injection drug use.*

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BACKGROUND

The HIV Epidemiology Research Study (HERS) was established as a prospective cohort in which to examine the outcomes of HIV disease in women with appropriate comparisons to a demographically and behaviorally similar group of uninfected women. Because women with HIV infection in the United States are most commonly from socioeconomically disadvantaged African American or Hispanic communities and often report a history of injection or crack cocaine drug use, HERS was designed to include all of these groups. These populations also have excess mortality risks unassociated with HIV infection.[1]

Several studies have demonstrated excess non-AIDS mortality among injection drug users,[2] but most of these studies did not include an HIV-uninfected comparison group, were conducted prior to the availability of effective antiretroviral therapy,[3–8] or were in non-US populations not comparable to disadvantaged minority populations in the United States.[8–11]

During the study period, the availability in the United States of effective antiretroviral medications increased dramatically, and the increasing use of highly active antiretroviral therapy (HAART) led to a significant reduction in AIDS diagnoses and AIDS-related mortality in several population samples.[12,13] However, compared to utilization in the Multicenter AIDS Cohort Studies (MACS) and HIV Outpatient Studies (HOPS) populations, the utilization of antiretrovirals has been lower in African Americans in the United States[14] and also lower in injection drug users.[15–18] Because HERS has significant numbers of both African American women and injection drug users, we examined the rates of mortality and causes of death among the HIV-infected and uninfected women in HERS over the years 1993–1999 to determine if these women are benefiting from mortality improvements that have been apparent in other groups in the United States.

METHODS

Cohort Study Design and Demographics

Between April 1993 and January 1995, four sites recruited 885 HIV-seropositive women (871 seroprevalent, 14 seroconverters) and 425 HIV-seronegative women at behavioral risk for HIV infection into the HERS Study: Brown University, Providence, Rhode Island; Montefiore Medical Center, Bronx, New York; the Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland; and Wayne State University School of Medicine, Detroit, Michigan. Two sites recruited primarily from clinics (Brown and Wayne State), while the other two sites recruited primarily from the community (Montefiore and Johns Hopkins). All participants were followed with scheduled semiannual interviews, physical exams, and specimen collection for laboratory testing and repository.[19] Women who reported a preexisting diagnosis of AIDS or were found to have clinical AIDS (by the pre-1993 definition) were not enrolled in the study; women with CD4+ cell counts less than 200 were enrolled.

At the time of entry into HERS, women were 16 to 55 years old (median, 35 years); were 58% African American, 24% white, 16% Hispanic, and 2% Asian, Native American, or other race/ethnicity. Also, 42% had not graduated from high school; only 16% were employed, and reported median household income was $9,000 per year. Finally, 68% had public insurance, and 19% reported no insurance.[20] By design, approximately one half (52%) reported injection drug use (IDU)

after 1985, and one half reported only a heterosexual exposure risk. Detailed illicit drug use questions were asked at each semiannual interview.

Predictor Variables

Measurement of CD4+ cell count by flow cytometry was done at each study visit using laboratories that underwent monthly checks through participation in the National Institute of Allergy and Infectious Disease quality assurance system. Plasma HIV RNA (viral load) was measured at each study visit using the branched-DNA assay (Quantiplex v2.0 and 3.0, Chiron Corp., Emeryville, CA). A woman was considered to have renal abnormalities if she had (a) a serum creatinine of 1.4 mg/dL or more, or urine protein level of 2+ or more, on any of the research visits through February 1997; or (b) an elevated serum creatinine or urinary protein from a medical records abstraction transcribed during the same time period. Hepatitis C antibodies were assessed by enzyme immunoassay (Abbott Laboratories) or enzyme-linked immunosorbent assay (Ortho Diagnostic Systems) on baseline or earliest available serum samples, as previously reported.[21] Hypertension and diabetes mellitus were defined as being present when hypertension or diabetes mellitus diagnoses were present in a medical record abstraction. Recent IDU was defined as reporting injection use of cocaine, heroin, or other opiates during the past 6 months. Crack cocaine use was defined as any use of crack cocaine during the past 6 months. Antiretroviral medication use was determined in face-to-face interviews every 6 months. The interview included both trade and generic names and color photographs of medications. Women were considered to be receiving HAART if it was reported to be currently taken at the time of the interview. HAART was defined as reported use of two specific reverse transcriptase inhibitors (NRTIs—AZT+ddI, 3TC+ddI, D4T+ddI, D4T+ddC, AZT+ddC, AZT+3TC) and one protease inhibitor; or one nonnucleoside reverse transcriptase inhibitor and two specific NRTIs; or Abacavir and AZT+3TC. All other combinations or monotherapies were considered non-HAART antiretroviral therapy (non-HAART ART).

Death Outcomes

In the HERS cohort, deaths that occurred by December 31, 1999 were ascertained and verified by death certificates, computerized searches of the National Death Index (NDI), and informant notification. When site staff were informed about a death by family, friends, or published obituaries, death certificates were requested from the local or state vital registrars. In addition, all sites conducted NDI Plus searches for participants known to have died or who had been lost to follow-up. Possible matches returned by NDI were processed at each site to determine if there was a true match (e.g., identical first and last name, social security number, and birth date). Death certificates were requested for all potential matches from NDI to obtain additional cause of death data for true matches and to verify or exclude potential matches.

Cause of Death

Cause of death was determined by examining all causes listed on the death certificate to determine the most likely underlying cause. If no death certificate was available, cause of death was assessed by examining the NDI cause of death, which was based on the death certificate available to NDI. HIV/AIDS-associated deaths had either one of the 24 AIDS-defining conditions[22] or simply "HIV/AIDS" as the underlying cause as defined above. Deaths were counted when provided by local infor-

mants, but no causes were attributed to deaths that did not have a death certificate basis. Deaths were classified due to unknown causes if no death certificate was located or if the NDI record provided no cause of death.

Statistical Analyses

Cox proportional hazards analysis was used to calculate mortality hazard ratios adjusted for all other variables. Baseline variables in the model were age at enrollment, hepatitis C (HCV) antibody status, and race. Clinical AIDS, CD4+ cell count, HIV RNA viral load, renal abnormalities, diabetes mellitus, hypertension, non-HAART ART, HAART, crack cocaine use, and IDU were entered as time-dependent variables. HIV seroconverters were included for the time they were HIV positive. The proportionality assumption was checked by evaluating the interaction between log (time) and one of the time-dependent variables. With only eight deaths in the HIV-uninfected cohort, multivariable regression analyses of risk factors would not have been productive.

The calculation of person-years (py) was based on the following: for deaths, the date of death for deaths with a death certificate or NDI match or the date of informant-reported death for those reported to have died without such verification; for censoring, the date of last study visit for those alive and still enrolled, or December 31, 1998 for those lost to follow-up prior to the last study visit and not determined to have died by the NDI match. SPSS 9.0 (SPSS, Inc., Chicago, IL) and SAS (SAS version 8.2, SAS, Inc., Cary, NC) were used to conduct all statistical analyses.

RESULTS

Selected baseline characteristics of the HERS cohort are shown in Table 1. It is noteworthy that none of the HIV-infected women were enrolled with a diagnosis of clinical AIDS and 61% of the HIV-infected women reported a history of injection drug use at baseline.

As of December 31, 1999, 242 deaths were known to have occurred in women enrolled in HERS: 233 (26.7%) of the prevalent HIV-infected women; 1 (7.1%) of the 14 women who seroconverted during the study; and 8 (1.9%) of the 425 women who remained HIV uninfected. Of the 242 deaths, 206 had valid death certificates, 20 deaths had NDI reports only, and 16 deaths were from local informants only. Deaths with a valid cause of death code were obtained from a total of 222 (92%) of the 242 deaths. 1996 was a transitional year for HAART availability and use. While 49 women (5.5%) reported HAART use in 1996, most of these reports occurred in the last four months of the year, with larger increases in HAART use occurring in 1997 and 1998. We chose 1997 as the beginning point of the HAART era for the purposes of this analysis.

Death Rates

Among the HIV-seropositive and seronegative women, mortality occurred at 5.2 deaths and 0.35 deaths per 100 py, respectively, over the entire observation period (Table 2). Overall death rates in the seropositive women were unchanged from the pre-HAART era (1993–1996) to the era of HAART availability (1997–1999)—(5.1 vs. 5.4 per 100 py, $P = .32$, Table 2). Table 3 shows that AIDS-defining death rates declined by 23% between the two time periods, and for women with a CD4+ cell count below 200/mm^3, death rates declined by 56% (9.7 in 1993–1996 to 4.3 per 100 py in 1997–1999, $P = .0002$). AIDS-defining deaths as a proportion of

TABLE 1. Baseline demographic and clinical characteristics of women in HERS

Variable	HIV infected (N = 885) N (%)	HIV uninfected (N = 425) N (%)
Age		
30 years or less	189 (21.4)	112 (26.4)
31–44	605 (68.4)	271 (63.8)
45 or greater	91 (10.3)	42 (9.9)
Race/ethnicity		
African American	538 (60.8)	225 (52.9)
White	183 (20.7)	134 (31.5)
Hispanic	152 (17.2)	62 (14.6)
Other	12 (1.4)	4 (0.9)
Clinical AIDS		
Yes	0 (0)	— —
No	885 (100)	— —
CD4+ cell count		
0–200	160 (18.1)	— —
>200–500	434 (49.0)	— —
>500	291 (32.9)	— —
RNA viral load* (copies/mL)		
<500	177 (20.5)	— —
500–10,000	474 (54.8)	— —
>10,000	213 (24.7)	— —
Ever injected drugs at baseline		
Yes	537 (60.7)	230 (54.1)
No	348 (39.3)	195 (45.9)
Renal laboratory abnormalities		
Yes	64 (7.2)	10 (2.4)
No	821 (92.8)	415 (97.6)
HCV antibody positivity*		
Yes	537 (61.4)	198 (47.5)
No	337 (38.6)	219 (52.5)

*Missing data affect cell counts for some variables.

deaths declined steadily in the last four years observed, from 30 deaths (58% of deaths in 1996) to 6 deaths (19% of deaths in 1999) (Table 3). AIDS-unrelated death rates increased by 31% over the same time period, from 2.4 to 3.5 per 100 py (Table 4).

During the period of observation, the use of any ART changed little, but among women receiving ART, the use of monotherapy declined significantly. From late 1996 on, the use of combination and Public Health Service-defined HAART regimens[23] increased, although to suboptimal levels. Adherence with HAART in this population was evaluated in a substudy of 175 HIV-positive HERS participants. Mean monthly adherence was less than 60%, and only 2% of the women had greater than 95% adherence over 6 months of follow-up.[24] Of women with study visits in the last 6 months of 1999 and who had CD4+ cell counts less than 200/mm^3, 41.5% were taking HAART, 27.4% were on non-HAART combinations, 2.8% were on monotherapy, and 28.3% were taking no antiretrovirals.

TABLE 2. All-cause mortality rates by time period

Time Period	Person-years of observation (py)	# Deaths	Mortality rates per 100 py
885 HIV-infected women			
1993–96	**2580**	**131**	**5.1***
1993	161	3	1.9
1994	825	26	3.2
1995	822	50	6.1
1996	772	52	6.7
1997–99	**1891**	**103**	**5.4***
1997	727	40	5.5
1998	692	32	4.6
1999	472	31	6.6
425 HIV-uninfected women			
1993–96	**1280**	**6**	**0.5****
1993	98	2	2.0
1994	341	3	0.9
1995	421	0	0.0
1996	420	1	0.2
1997–99	**993**	**2**	**0.2****
1997	418	1	0.2
1998	417	0	0.0
1999	158	1	0.6

*Fisher's exact test, $P = 32$; no significant difference in the all-cause mortality rates between 1993–96 and 1997–99.

**Fisher's exact test, $P = .48$; no significant difference in the all-cause mortality rates between 1993–96 and 1997–99.

TABLE 3. AIDS-defining mortality rates by time period and CD4+ cell count, 885 HIV-infected women

	All HIV-infected Women		HIV-infected Women with CD4+ cell counts <200 at any time in a year	
Time Period	# AIDS deaths	Mortality Rates	# AIDS deaths	Mortality Rates
1993–96	**68 (51.9)†**	**2.6***	**54**	**9.7****
1993	2 (67)		—	
1994	14 (54)		7	
1995	22 (44)		18	
1996	30 (58)		29	
1997–99	**37 (35.9)**	**2.0***	**34**	**4.3****
1997	15 (38)		14	
1998	16 (50)		15	
1999	6 (19)		5	

*Fisher's exact test, $P = .09$ for mortality rates 1993–96 vs. 1997–99.

**Fisher's exact test, $P = .0002$; for mortality rates 1993–96 vs. 1997–99.

†Percent of all-cause deaths.

TABLE 4. Non–AIDS-defining mortality rates by time period, 885 HIV-infected women

Time period	# non-AIDS deaths	Mortality Rates
1993–96	**63 (48.1)**	**2.4***
1993	1 (33)†	
1994	12 (46)	
1995	28 (56)	
1996	22 (42)	
1997–99	**66 (64.1)**	**3.5***
1997	25 (62)	
1998	16 (50)	
1999	25 (81)	

*Fisher's exact test, $P = .03$ for mortality rates in 1993–96 vs. 1997–99.

†Percent of all-cause deaths.

Mortality Risk Factors

Table 5 presents the Cox model adjusted mortality hazard ratios for risk factors of deaths due to AIDS-defining causes and non-AIDS causes, separately. When deaths were restricted to the 105 AIDS-defining deaths, the effect of HAART was strong (relative hazard [RH_{adj}] = 0.25, $P = .003$), but the effects of both HCV positivity ($RH_{adj} = 0.94$, $P = .76$) and recent injection drug use ($RH_{adj} = 0.72$, $P = .35$) diminished. When deaths were restricted to 129 non–AIDS-defining or undetermined deaths, the effect of HAART use was nonsignificant ($RH_{adj} = 1.0$, $P = .97$), but the effect of HCV positivity ($RH_{adj} = 2.6$, $P = .0002$) and recent injection drug use ($RH_{adj} = 1.7$, $P < .02$) became more important. Clinical AIDS, CD4+ cell count less than 200/mm^3, and renal abnormalities were the only factors significantly associated with both AIDS-defining and non–AIDS-defining mortality. Smoking crack cocaine was not significantly associated with either AIDS-defining or AIDS-unrelated mortality. Study site was not significantly associated with AIDS-defining or with non–AIDS-defining mortality.

Death Certificate Analysis

Table 6 shows a breakdown of the causes of death in 234 HIV-infected women and 8 HIV-uninfected women. Of all deaths in HIV-infected women, 45% (105/234) occurred from AIDS-defining causes. Of the 234 total, 63 (27%) died of "AIDS" without notation on the death certificate of specific causes or conditions currently included in the CDC AIDS case definition, 16% died of AIDS-defining opportunistic infections (including 4 cases of pneumocytis pneumonia and 22 cases of other pneumonias), and 2% died of AIDS-defining cancers.

Further, 47% (109/234) of deaths in HIV-infected women occurred from causes not attributed to AIDS: 18 (8%) from sepsis, 18 (8%) from other non–AIDS-defining infections, 18 (8%) from drug overdoses, 10 (4%) from liver causes, 10 (4%) from cardiovascular disease, 9 (4%) from trauma, 8 (3%) from non–AIDS-defining cancers, 6 (2.6%) from hematological causes, 5 (2%) from renal causes, and 7 (3%) from miscellaneous other causes. For the remaining 20 deaths

TABLE 5. Factors associated with mortality, 885 HIV-infected women in the HERS cohort

	AIDS-defining causes		Non–AIDS-defining causes	
Variable	Relative hazards, 95% confidence interval*	*P*-value	Relative hazards, 95% confidence interval*	*P*-value
Age (for each increase of 10 yrs)	1.5 per 10 years (1.1, 2.1)	.009	0.9 per 10 years (0.7, 1.3)	0.77
Clinical AIDS	7.7 (5.0, 11.8)	<.0001	1.9 (1.1, 3.1)	0.01
CD4+ cell count <200 vs. >500	24.2 (3.2, 181.8)	.002	2.3 (1.2, 4.1)	.008
CD4+ cell count 200–500 vs. >500	5.6 (0.7, 43.3)	.09	1.3 (0.8, 2.3)	.31
Plasma HIV RNA 500–10,000 vs. <500 copies/mL	1.7 (0.8, 3.6)	.49	1.9 (0.8, 4.2)	.13
Plasma HIV RNA >10,000 vs. <500 copies/mL	5.9 (0.8, 44.3)	.08	2.6 (1.1, 5.9)	.008
HCV antibody positivity	0.9 (0.6, 1.4)	.76	2.6 (1.6, 4.2)	.0002
Renal abnormalities	2.6 (1.7, 3.9)	<.0001	2.7 (1.9, 4.0)	<.0001
Diabetes mellitus	1.8 (0.4, 7.4)	.44	2.2 (0.9, 5.3)	.07
Hypertension	1.0 (0.5, 2.1)	.98	2.5 (1.4, 4.3)	.002
HAART† use vs. no ART	0.2 (0.1, 0.6)	.003	1.0 (0.6, 1.7)	.97
non-HAART ART† vs. no ART	0.8 (0.5, 1.3)	.42	0.8 (0.5, 1.2)	.34
Crack use last 6 months	1.3 (0.8, 2.3)	.32	0.7 (0.4, 1.2)	.18
Injection drug use last 6 months	0.7 (0.4, 1.4)	.35	1.7 (1.1, 2.7)	.02

*Adjusted for all other variables listed, by Cox proportional hazards model.
†HAART, highly active antiretroviral therapy; ART, antiretroviral therapy (not HAART).

(20/234, 8%), deaths were reported but no documentation of the cause of death was available at the time of this analysis.

Illicit Drug Use–Associated Deaths

Table 7 shows the proportions of deaths related to the consequences of illicit drug use. Of the 36 deaths in seropositive women due to infections, 25 were from endocarditis or sepsis. Combining these 25 with the 9 (hepatitis B and C) chronic hepatitis–related deaths and the 18 overdose deaths gives 52 illicit drug–related deaths. Altogether, 48% (52/109) of non–AIDS-defining deaths were attributable to consequences of illicit drug use in HIV-seropositive women. Of the eight deaths among seronegative women, most (6/8 or 75%) were attributable to illicit drug use as either overdose (five deaths) or hepatitis C–related chronic hepatitis (one death).

DISCUSSION

Overall mortality rates in the HIV-infected women in this cohort were unchanged between the period prior to HAART availability, 1993–1996, and the period when HAART became available, 1997–1999. In contrast, the AIDS-defining-causes death rate declined by 23% overall, and by 56% in women with a CD4+ cell count less than 200 mm^3, over the same time period. A high proportion of the deaths in the HIV-infected women were due to non–AIDS-defining causes (47%), compared to

TABLE 6. Categorical causes of death by HIV status, HERS cohort, 1993–1999

	HIV infected (N = 234) # deaths (%)	HIV uninfected (N = 8) # deaths (%)
AIDS-defining causes	105 (44.9)	
AIDS-defining infection	37 (15.8)	—
AIDS-defining cancer	5 (2.1)	—
AIDS/Other*	63 (26.9)	—
Not AIDS-defining causes	109 (46.6)	8 (100)
Sepsis	18 (7.7)	0
Other non-AIDS infections	18 (7.7)	0
Cancer	8 (3.4)	0
Cardiovascular	10 (4.3)	2 (25)
Liver	10 (4.3)	1 (12.5)
Renal	5 (2.1)	0
Hematological	6 (2.6)	0
Trauma	9 (3.9)	0
Drug overdose	18 (7.7)	5 (62.5)
Other†	7 (3.0)	0
Undetermined cause	20 (8.5)	0

*HIV listed as a cause of death, but not otherwise specified.
†E.g., cardiopulmonary arrest, pancreatitis.

AIDS-defining causes (45%). The proportion of deaths due to AIDS-defining causes declined steadily from 1996 through 1999. The significant association of HAART use with mortality from AIDS-defining deaths suggests that much of the decline in AIDS-related mortality is, as expected, attributable to increasing use of HAART. The association of increased HAART use and declines in HIV/AIDS causes or mortality rates has been reported in other population studies.[12,13] However, the 70% to 90% levels of use of HAART reported in populations with fewer IDU-associated HIV cases[13,25] were not seen in the HERS population, where by 1999 only 42% who met reasonable clinical criteria were using HAART. Two factors that distinguished the HERS population in addition to the IDU and the high proportion of racial and ethnic minorities were unemployment and poverty: only 16% were employed, and the average (reported) household income was $9,000 per year at enrollment.

The risk factor analysis showed many factors that contributed to mortality.

TABLE 7. Illicit drug-related deaths by HIV status, HERS cohort, 1993–1999

	HIV-infected Number (%)	HIV-uninfected Number (%)
All non–AIDS-defining causes	109 (100)	8 (100)
Illicit drug–associated	52 (48)	6 (75)
Sepsis and endocarditis	25	0
Hepatitis B and C infections	9	1
Drug overdose	18	5
Other causes	57 (52)	2 (25)

AIDS was the strongest predictor of mortality, but we also found that a number of comorbidities were important independent predictors of mortality, including renal abnormalities, hepatitis C antibody positivity, hypertension, and diabetes mellitus. The effect of hepatitis C antibody positivity and IDU on mortality was clearly evident for the non–AIDS-defining causes, from both death certificate causes, and from the regression analysis of mortality risk factors. Although HAART use was associated with decreased all-cause mortality, the (negative) association was entirely attributable to its association with the 105 AIDS-related deaths.

By design, at least 50% of these women had injected drugs since 1985. That 61% of HIV-infected women had a history of drug use surely contributed to the 48% of all non–HIV-related deaths being from drug overdoses and non–HIV-defining infections (eg., bacterial endocarditis, sepsis, and hepatitis B and C infections).

Increases in the proportion of deaths due to causes other than AIDS over time have also been reported in a few case series studies[26–30] and an observational cohort.[31] While based only on serial cross-sectional death data, nevertheless, the changes in cause of death distribution in a facility where three quarters of the HIV cases were due to IDU are remarkably similar to HERS.[27] In that case series, the percentage of deaths due to AIDS-defining causes dropped from about 70% in 1996 to 27% in 1999; liver disease and sepsis causes increased from 28% in 1996 to 64% in 1999. Cause-specific data from HERS and these other sources indicate that even as HIV/AIDS-related mortality rates decline, in populations with heavy proportions of drug users, effects of illicit drug use can offset declines in deaths due to increasing use of HAART. Unlike the results observed in HERS, the Women's Interagency Cohort Study (WIHS) reported overall mortality rates significantly declined and rates due to non-AIDS causes unchanged over 1995 to 2000.[32] The total proportion of non-AIDS causes of death was much lower in the WIHS (20%) than in the HERS women (47%), which may have been attributable to different IDU histories—39% in WIHS and 61% in HERS.

The small number of AIDS-defining cancer deaths in this cohort is reassuring for concerns about gynecologic cancers, as all but one were from lymphomas. The increased rates of incident lymphoma but not cervical cancer after 1982 in African American compared to white women in New York and New Jersey has been previously reported.[33] All women in the HERS study received Pap smears at their semiannual visits, with prompt referral of women with abnormal smears for further assessment by colposcopy and biopsy and treatment, if indicated. There was a high prevalence of cervical dysplasia and human papillomavirus infection[34] in this cohort. Nevertheless, despite the occurrence of five incident cases of cervical cancer,[35] cervical cancer did not contribute significantly to mortality, possibly in part because of aggressive identification and follow-up of precursor and early cancer lesions. Of the five cases of cervical cancer, only one woman in the cohort died of this disease.

Choosing the beginning of the HAART era is not an exact science. Studies have used 1997, 1996, or earlier depending on historical availability in their area.[36] An unavoidable limitation of these data is that we necessarily relied on the death certificates to establish AIDS-defining and non–AIDS-defining deaths. Death certificates' weaknesses are famous and well studied.[37–39] Better physician training in correct sequencing of events from immediate to underlying cause of death has been suggested.[40] Over half of the AIDS-related deaths in these data gave no additional information beyond a single entry of HIV as cause of death. With more complete information, some of these "AIDS/not otherwise specified" cases would likely have

been reclassified as AIDS-unrelated deaths; therefore the numbers of AIDS-unrelated deaths we reported are probably conservative. Nevertheless, our conclusions about the role of HAART and illicit drug use are supported by the cause-specific multivariable regression models and the enumeration of specific causes. We are not aware of any major changes in the accuracy of death certificate reporting that occurred during the period of our analysis.

In summary, mortality rates among the women in the HERS cohort were, as expected, significantly lower in HIV-uninfected women than among their HIV-infected peers. Because HAART use was relatively low and because so many women were injection drug users, mortality rates did not decline in the several years of study, but progressively were more attributable to IDU-related complications—such as drug overdose, hepatitis virus infections, bacterial endocarditis, and sepsis—and fewer with AIDS-defining conditions. The finding of such a large percentage of illicit drug-related causes in these women, and that most women were economically disadvantaged, strongly supports the concept of integrating HIV care and drug treatment programs more effectively.

APPENDIX

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